Memorandum

To: STN 100300/5000

Through: Paul Richman, PhD
Chief, Bacterial, Parasitic, and Allergenic Products Branch
Division of Vaccines and Related Products Applications

From: Julianne C.M. Clifford, PhD, and Review Committee Chair

Date: April 12, 2002

Re: Approval recommendation for STN 1003000/5000 submitted by Allergan, Inc. to use Botulinum Toxin Type A (BOTOX COSMETIC) for treatment of glabellar facial lines.

Background

Allergan's Botulinum Toxin Type A (BOTOX) product was approved in 1991 for the treatment of blepharospasm and strabismus. In December 2000, Allergan received approval under a Supplement to their Biologic License for the new clinical indication of treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia.

On January 16, 2001, Allergan Inc. (Sponsor) filed a new Supplement (STN 10300.5000) in support of the addition of another new clinical indication to their Biologic License for BOTOX (Botulinum Toxin Type A), namely, the treatment of glabellar facial lines. This submission contained 1) the final study reports for two Phase 3, randomized, double-blind, placebo-controlled, multi-site clinical trials of identical design which evaluated the safety and effectiveness of BOTOX compared to saline placebo administered in a single treatment session; 2) the final study report for an open-label, follow-on treatment, safety study for which subjects of the randomized studies were eligible for enrollment and which evaluated the safety of open-label administration of BOTOX in 2 sequential treatment sessions, 3 months apart, with a minimum of 120 days of follow-up after each session; 3) the Integrated Summary of Safety and Integrated Summary of Efficacy reports; and 4) administrative components including a request for a waiver from the requirement to assess the safety and efficacy of the product for this indication in pediatric populations. The design and nature of the three clinical trials conducted under an Investigational New Drug Application filed with FDA/CBER, were agreed upon in pre-IND and IND stage deliberations between CBER and the Sponsor. Typically, Phase 1 and 2 clinical trails provide the scientific basis for selection of dose, dosing regimen, primary efficacy endpoint measures and other components of a Phase 3 pivotal study. However, agreement was reached between CBER and the Sponsor that

sufficient information was available from previously conducted non-IND studies and published literature accounts to support the proposed study designs, efficacy endpoints and dose to be evaluated in the Phase 3 studies.

Upon completion of the discipline reviews (clinical, dermatological consult, statistical), the Review Committee discussed the review findings and determined the information in the file to be supportive of an approval for a new clinical indication of temporary reduction in the severity of glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age. However, the Review Committee found the Sponsor's proposed labeling for this new indication to be significantly deficient in content.

Allergan filed both a Response to the Complete Response letter and an Amendment to the File on November 23, 2001. The Response consisted of revised labeling that incorporated the Review Committee's CR letter comments and revisions and included draft Adverse Event Tables for consideration by the Review Team. In preparation of those tables, Allergan recognized errors in the originally submitted Integrated Summary of Safety and filed a Revised Integrated Summary of Safety as an Amendment to the Supplement on the same date as the Response to the Complete Response Letter. The Review Committee found the Response submission alone to be Incomplete as it did not provide a means of verifying the data presented in the proposed Adverse Event tables. However, the simultaneous filing of the Amendment containing the Revised Integrated Summary of Safety did provide the needed information and the Review Committee concluded that, in combination, these submissions consisted a Complete Response to a Complete Response Letter.

Allergan submitted draft Package and Container labeling on March 22, 2002. Upon review and consult with the Advertising and Promotional Labeling Branch, the Committee Chair requested, by teleconference, that Allergan insert "For Single Patient Use" on the side panel of the Package Label.

Upon completion of the Committee's review of Allergan's revised draft labeling (Package Insert) and the revised Integrated Summary of Safety, the Review Committee returned further comments and labeling revisions to Allergan on March 26, 2002. On March 28, 2002, Allergan submitted a response that incorporated all of the Committee's revisions. Allergan also submitted a letter to the File providing a written commitment to file a report of post-marketing adverse event surveillance data covering 12 months of marketing of BOTOX COSMETIC and to review the Package Insert for revisions based upon that report. Allergan also committed to revising the Package Label as had been requested by Dr. Clifford (Committee Chair).

On April 8, 2002, Allergan submitted a Draft Package Insert for BOTOX COSMETIC that incorporated all revisions agreed upon by the Sponsor and the Review Committee. On April 9, 2002, Allergan submitted Draft Package Labeling incorporating the Review Committee's request for the phrase "For Single Patient Use" on the side panel.

Clinical Development Plan and Clinical Trials

[redacted] CBER concerns focused upon three issues: 1) sufficient data to assess the safety of this product in a non-therapeutic, non-life-threatening clinical indication in a single treatment session, 2) sufficient data to assess potential adverse effects of continued use or multiple treatment sessions since the marketed use of BOTOX for this new indication is expected to mirror the therapeutic indications wherein patients are treated at 3-4 month intervals, and 3) sufficient data to assess reproductive and/or developmental toxicities since the anticipated marketing population for this indication will be primarily women of child bearing ages. The CBER Review Team included in its considerations International Committee on Harmonization Guidance Document entitled: "Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions". This document includes recommendations pertaining to the number of patients that should be exposed to the drug treatment for during short-term evaluations (6months) and longer-term (12 months or more) evaluations of safety.

An agreement was reached between CBER and the Sponsor that the clinical development plan for this new indication would consist of three clinical trials to be conducted under an Investigational New Drug Application. Two of these trails were multicenter, randomized, double blind, placebo-controlled studies to evaluate the safety and efficacy of BOTOX administered at a pre-determined total dose level at specified injection sites. The third trial was an open-label study to assess safety of the product when administered for a minimum of 2 treatment sessions. (See reviews by Dr. Kleppinger and Dr. Zhen for a more detailed description of the study design, conduct and analyses of the study results.)

The double blind studies were conducted at 29 sites in the United States and 1 in Canada. The studies enrolled healthy adults (ages 18 to 75 years) with glabellar lines of at least moderate severity at maximum frown. Each study subject was scheduled to receive a single treatment of either BOTOX (n = 405, combined studies) or placebo (n= 132, combined studies) as an injection volume of 0.1ml/injection site, for a dose/injection site of 4U (BOTOX). Patients were to be injected in 5 sites, 1 in the procerus and 2 in each corrugator supercilii, for a total dose of 20U (BOTOX). Most of the study subjects were female (81.9%) and Caucasian (83.8%) and the mean age was 46 years with a range of 22 to 78 years. Of these, 68.2% were $\leq$ 50 years of age, 31.8 % were $\geq$ 51 years and 6% were $\geq$ 65 years of age. The co-primary efficacy endpoints for these studies were the Investigator's rating of glabellar line severity at maximum frown at Day 30 after injection and the Subject's Global Assessment of change in appearance in glabellar lines at Day 30 after injection. A photoguide was provided to each study center to assist in the Investigators' grading of glabellar line severity using a 4-point grading scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). A "responder" was defined as a subject having a severity grade of 0 or 1.

For the Subject's Global Assessment of change in appearance, the subjects responded to the question: "How would you rate the change in the appearance of your glabellar lines compared with immediately before your most recent injection?" The ratings of responses by subjects were from +4 (complete improvement, about 100% improvement) to –4 (very marked worsening, about 100% or greater). For the Subject's Global Assessment, a "responder" was defined as a subject having a grade of at least +2 (moderate improvement, about 50% improvement). A secondary efficacy endpoint was the Investigator's rating of glabellar line severity at rest on Day 30 post injection in those subjects who at baseline demonstrated a glabellar line severity score at rest of moderate or severe. For the Investigator's rating, the criteria for effectiveness was a 30 percentage point difference between BOTOX COSMETIC and placebo treatment groups in the incidence of subjects with Investigator's rating of glabellar line severity of none to mild at maximum frown. For the Subject's Global Assessment, the criteria for effectiveness was a 25 percentage point difference between BOTOX COSMETIC and placebo treatment groups in the incidence of subjects with a score of at least +2 (moderate improvement) in the subject's assessment of change in the appearance of glabellar lines.

In the double-blind studies, the severity of glabellar lines was reduced for up to 120 days in the BOTOX COSMETIC group compared to the placebo group as measured both by investigator rating of glabellar line severity at maximum frown and at rest, and by subject's global assessment of change in appearance of glabellar lines. By Day 7, 74% (299/405) of subjects had achieved a severity score of none or mild at maximum frown by the investigator's assessment. This increased to 80% (325/405) by the primary efficacy endpoint day of Day 30, compared to 3% of placebo-treated patients. By Day 7, 83% (334/405) of subjects assessed moderate or better improvement in their own appearance (+2 or better). This increased to 89% (362/405) by the primary efficacy endpoint day of Day 30, compared to 7% of placebo-treated patients. Based on resting appearance as judged by the investigator, 68% (110/161) of subjects achieved a severity

score of none or mild at Day 7, and 74% (119/161) by the efficacy endpoint day of Day 30.

The responder rates for both co-primary efficacy variables were higher for subjects ≤ 50 years of age than for those ≥ 51 years to ≤ 65 years of age. Efficacy was higher for both groups compared to those subjects ≥ 65 years of age. In the cervical dystonia trial, there was also a consistently observed treatment-associated effect between subsets greater than and less than 65 years of age. There were no statistically significant between-group differences for the investigator's assessment at maximum frown for this age group. There was a statistically significant difference in favor of BOTOX COSMETIC for the subject's global assessment at all time points except Day 120 ($p \leq 0.036$). Exploratory analyses of subsets by patient gender suggest that both genders receive benefit, although female patients may receive somewhat greater amounts than male patients. The responder rates for both co-primary efficacy variables were higher for female subjects than for males. There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets. The responder rates for both co-primary efficacy variables were slightly higher for Caucasian than for non-Caucasian subjects.

On completion of the double-blind studies, participants were invited to participate in the multicenter, open-label, non-comparative study to evaluate the safety of repeated treatments with BOTOX COSMETIC using the same dose and procedure from the previous studies. Only patients who had a glabellar line severity rating of mild or greater at maximum frown at the time of enrollment were admitted to the open-label safety evaluation study. A total of 373 subjects (72.6%) were enrolled in this open-label study and 318 subjects completed the study. There were a total of 258 subjects who received BOTOX COSMETIC in the previous trials and both injections of BOTOX COSMETIC during this trial (for a total treatment time of 12 months). Of these, 239 subjects completed the 120 days of follow-up after the final injection. The open-label study was designed specifically to evaluate the safety of repeated treatments. In the open-label, repeat injection study, blepharoptosis was reported for 2.1% (8/373) of subjects in the first treatment cycle and 1.2% (4/343) of subjects in the second treatment cycle. Adverse events of any type were reported for 49.1% (183/373) of subjects.

In clinical trials described above the most frequently reported adverse events following injection of BOTOX COSMETIC were headache, respiratory infection, flu syndrome, blepharoptosis and nausea. Less frequently occurring (<3%) adverse reactions included pain in the face, erythema at the injection site and muscle weakness. While local weakness of the injected muscle(s) is representative of the expected pharmacological action of botulinum toxin, weakness of adjacent muscles may occur as a result of the spread of toxin. These events are thought to be associated with the injection and occurred within the first week. The events were generally transient but may last several months. In the double-blind studies, adverse events of any cause were reported for 43.7% of the BOTOX COSMETIC treated subjects and 41.5% of the placebo treated subjects. The incidence of blepharoptosis was higher in the BOTOX COSMETIC treated arm than in placebo (3.2% vs. 0%, p-value = 0.045). In the open-label, repeat injection

study, blepharoptosis was reported for 2.1% (8/373) of subjects in the first treatment cycle and 1.2% (4/343) of subjects in the second treatment cycle. Adverse events of any type were reported for 49.1% (183/373) of subjects overall. The most frequently reported of these adverse events in the open-label study included respiratory infection, headache, flu syndrome, blepharoptosis, pain and nausea.

Reproductive Toxicity

In response to the Review Committee's concerns regarding an assessment of the reproductive toxicity of BOTOX,

Product and Manufacturing Issues

There were no product manufacture, production facility or lot release issues to be addressed within the context of this Supplement.

Post Marketing Commitments

Allergan has committed to review the post-marketing adverse event surveillance data after one year of commercial distribution for this indication and to propose revised labeling as warranted.

Allergan recognizes that further revisions may be warranted pending final review of the toxicology reports submitted on March 4, 2002, to IND

Pediatric Studies

Allergan has requested a waiver for pediatric studies per 21 CFR 601.27 for the age groups from 0 to 16 years. Allergan's request and justification have been considered by the Review Committee.

Committee Recommendation

It is the recommendation of the Review Committee that this Biologic License Supplement (STN-103000.5000) submitted by Allergan, Inc. for (Botulinum Toxin Type A) for the addition of new clinical indication be approved.

Under this approval, Botulinum Toxin Type A (BOTOX COSMETIC) is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients $\leq$ 65 years of age. Under prior approvals, BOTOX is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above and treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia.